VALUE IN HEALTH 14 (2011) 679–686

available at www.sciencedirect.com

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Impact of Drug Treatment History on Comparative Effectiveness Research in Schizophrenia

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A B S T R A C T

Objectives: Randomized clinical trials frequently attract volunteer patients who were either non-compliant or seeking to switch therapies. Patients on active therapies often undergo a washout period after which a single medication is initiated. Observational research has the potential to compare alternative treatments under a wider range of clinical situations if care is taken to document each patient's treatment history. **Methods:** This study used paid claims data from a large commercial insurer to investigate drug therapy outcomes in schizophrenia. Episodes of drug therapy were defined each time a patient initiated or restarted drug therapy using an antipsychotic, antidepressant or mood stabilizing medication. Episode definitions were based on calculations of continuous drug therapy using a 15-day gap definition. A total of 21,570 episodes of drug therapy were included in the analysis, some of which used two drugs as initial therapy. **Results:** Most episodes were initiated using a mood stabilizing drug (27%) or an antidepressant (38%). Over 62% of all episodes were augmentation therapy in which a psychotropic drug was added to an existing psychotropic medication, followed by switching episodes (22%) and restart episodes (16%). Patient outcomes measured by either duration of uninterrupted therapy or one-year post-treatment cost varied significantly with patient treatment history, especially episode type. The comparative effectiveness of alternative therapies is sensitive to the extent to which treatment history is taken into account. **Conclusions:** Observational comparative effectiveness research should capture and evaluate patient outcomes across a wide range of patients taking into account the patient's treatment history.

Keywords: comparative effectiveness research, schizophrenia, treatment history.

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Introduction

Research using retrospective data base analyses can significantly improve our understanding of the comparative, real-world effectiveness of alternative therapies. In particular, real world data include patients that span the full range of disease severity, co-morbidity profiles and treatment history who are typically excluded from well controlled, prospective clinical trials. Observational research, however, also has significant limitations. Real-world patients are not randomly assigned to treatment which creates significant heterogeneity across alternative treatments. To reduce heterogeneity, many retrospective data base studies mimic clinical trials and focus on a narrow sub-population for study. Many of the inclusion and exclusion criteria use in these studies are based on treatment history. For example, researchers often limit retrospective comparative effectiveness studies to patients who have not used study medications for significant periods of time. These extended "washout" periods are particularly restrictive when studying chronic illnesses, such as severe mental illness, for which achieving effective long-term drug therapy is difficult and an individual patient may have initiated multiple attempts at drug therapy during a multiple-year data period.

There are alternatives for improving the internal validity of retrospective data base analyses without artificially narrowing the range of patients to be studied. Specifically, the potential bias created by heterogeneity across alternative treatment groups can be mitigated by creating a more complete set of independent variables that are correlated to treatment selection and patient outcomes. While paid claims data have some important limitations in this regard, such as missing clinical data, claims data are well suited for documenting the medical history of the patient prior to treatment, including diagnosis, prior use of health services and the patient's drug treatment history using the medications under study. Moreover, including all patient episodes regardless of the drug use history at the time of treatment initiation allows the research to investigate comparative effectiveness across the full range of patients treated under real-world clinical conditions.

The patient's drug treatment history may be particularly important for patients with severe mental illnesses. Two recently published studies by Chen, McCombs, and Park [1,2] have reported that medication compliance and the cost of treating patients with schizophrenia in the California Medicaid Program (MediCal) varied significantly with the patient's treatment history. Specifically, patients switching medications or augmenting an existing treatment regimen displayed significantly longer time to all-cause discontinuation (TTAD) and the highest post-treatment cost over 1 year when compared with patients restarting a therapy used previously. Other treatment history variables were also significant pre-

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doi:10.1016/j.jval.2011.02.002

dictors of patient outcomes. For example, patients initiating combination therapy and duration of therapy on the previous episode were positively correlated with TTAD, whereas the number of treatment attempts in the year prior to starting a new episode was negatively correlated with TTAD.

Chen, McCombs, and Park [1,2] also documented that the comparative effectiveness comparisons of atypical antipsychotics to conventional medications were sensitive to patient treatment history. The atypical antipsychotics were associated with reductions in the cost of medical services that partially offset the higher cost of these medications with the exception of patients switching therapy without a break in treatment. The study also found that patients using atypical antipsychotics achieved longer TTAD relative to patients using typical antipsychotics (TAP). These latter results were consistent with previous, more restrictive studies using either retrospective paid claims data [3–5] or data from prospective trials designed to more closely approximate real-world clinical practice [6,7].

The importance of treatment history in determining patient outcomes and the differences in treatment history across alternative drugs raises concerns about bias in retrospective database studies that do not explicitly control for treatment history. Marshall and McCombs [8] investigated this issue using the MediCal data for patients with schizophrenia. This study demonstrated that comparisons of TTAD were sensitive to the exclusion of patient treatment history. However, the atypical antipsychotics consistently dominated conventional medications with regard to patient compliance while there were small changes in the comparisons between the newer medications.

This research used paid claims data from a large commercial insurer in the United States to investigate the impact of patient treatment history on a wide range of patient outcome measures for patients with schizophrenia. First, the differences in treatment history across alternative medications are documented. Next, the analyses estimates impact of treatment history on TTAD and costs over the first post-treatment year by type of service. Finally, estimates of head-to-head comparative effectiveness analyses across alternative therapies are compared using model specifications with and without treatment history variables.

Methods

Data

This research used paid claims data from a large commercial insurer in the United States that offered a wide range of insurance products (commercial, Medicare, Medicaid), plan designs (HMO, point of service, PPO, exclusive provider organizations, indemnity plans), and drug formulary structures to members across the United States. The data period was June 2003 to May 2006 and included both medical and prescription drug claims. Patients with schizophrenia were identified based upon finding an ICD-9 diagnosis code for schizophrenia (295.xx) recorded in their paid claims history. The unit of analysis is the treatment episode, which is broadly defined to include all available drug therapy attempts initiated by patients during the data period using antipsychotics, mood stabilizers or antidepressants. Four types of episodes were defined initially based on whether or not the patient was on active therapy when a new treatment attempt was initiated and whether or not the patient was changing therapies.

Definition of continuous therapy

A key element in this research is the definition of continuous drug therapy which was used to differentiate between treatment episode types. Duration of therapy was defined as a continuous use of a medication up to a gap of greater than 15 days between the end of estimated days-of-supply and the next prescription refill. The estimated days of supply was set equal to the sum of the reported days supply on the prescription claim and a running count of "unused" days of supply that a patient may have on hand due to the early refill of previous prescriptions. The sum of unused days of supply was capped at 30 days. TTAD was calculated for each individual medication and across all psychotropic medications used by the patient so long as no gap in drug therapy greater than 15 days appeared as patients switched therapies. The 15-day gap is consistent with findings by Weiden et al. [9] that the risk of hospitalization increased significantly in patients with schizophrenia after breaks in therapy as short as 10 days. Patients may have multiple episodes on one medication and/or across multiple medications.

Unit of observation

The unit of observation for the analyses was the drug treatment episode. Four types of treatment episodes were defined based on two elements derived from the patient's treatment history at the time a new treatment attempt was initiated: 1) whether or not the patient was changing medications, and 2) whether or not the patient was on active therapy. Both elements of treatment history were based on the medications used in patient's most recent prior episode and the duration of uninterrupted therapy achieved based on a 15-day gap in drug availability.

First observed episode

By definition, each patient has one "first" episode of psychotropic drug therapy recorded in the available data set. Many of these first episodes appear at the beginning of the data period and include multiple drugs making it likely that these are continuing episodes initiated in the time period prior to the data period. Nevertheless, even using multiple years of data and screening episodes for period of data prior to the episode start date, it is impossible to determine whether or not the first observed episode for a patient is truly the first time a patient used a psychotropic medication. Therefore, the initial treatment episode observed for each patient was excluded from further analysis.

Restart episodes using the same medication

Restart episodes were defined when the patient was not on active drug therapy and initiated therapy with the medication used in their most recent prior treatment attempt.

Switching episodes

A switching episode was defined when a patient changed medication. If the patient was on active therapy at the time a new psychotropic medication was initiated, all previous medications had to be discontinued within 60 days.

Augmentation episodes

An augmentation episode was defined when a patient added a "new" therapy without a break in therapy and continued to purchase one or more of their previous psychotropic medications beyond 60 days.

Other elements of treatment history

Several additional variables were created from the data that reflect on the patient's treatment history at the time that a new episode of therapy was initiated. These variables were used as independent variables in the analyses of TTAD and post-treatment cost. Patients initiating therapy using two or more new medications were defined as initiating combination therapy. The mix of psychotropic drugs used in the prior 6 months was also documented as dichotomous variables, including the use of depot formulations as a separate category using data from all previous treatment at-

tempts. Finally, a count of prior treatment episodes initiated in the prior 6 months was abstracted from the data.

Inclusion and exclusion criteria

Once all of the episodes of care included in the available data were created, the following inclusion and exclusion criteria were then applied to each episode:

1. Patient episodes must include a minimum of 180 days of patient eligibility prior to the date the treatment episode was initiated.
2. Patient episodes must include a minimum of 360 days (12 months) of data following the initiation of treatment.
3. Patients were at least 10 years of age at the time treatment was initiated.
4. Patient episodes with more than $500,000 (USD) in total cost prior to or following the initiation of therapy were excluded (0.14% of all schizophrenia and bipolar patients).
5. Patient episodes with negative cost prior to or following the initiation of treatment were excluded. Negative cost values were generated if the patient's paid claim file included an adjustment claim correcting for prior overpayments due to problems such as duplicate claims.
6. Patients with a history of nursing home use or hospice care were excluded from the analysis.
7. The first observed episode of treatment for each patient was excluded due to the ambiguity concerning the patient's drug treatment history.

Patient outcome measures

The patient outcome measures for this research project are broken down into two categories, each of which includes multiple outcome measures. Drug therapy outcome measures include days of uninterrupted drug therapy on the initial drug and on all psychotropic drugs so long as changes in therapy are accomplished without a break in therapy, and time to a change in medications (switch or augmentation). Health-care cost variables were measured by summing the amount charged on the paid claim during the first post-treatment year broken down by type of service and time to hospitalization. The amount charged includes any deductible or copayment obligations of the patient, but may overstate the payment from the insurance company that did not make allowed charge data available.

Independent variables

The development of an exhaustive list of independent variables for inclusion in the multivariate statistical models is the first line of defense against treatment selection bias in non-randomized studies that compare patient outcomes and costs across alternative treatment options. This study developed independent variables related to patient demographics, medical and mental health diagnostic profiles of the patient, and prior use of health-care services by type of service. Information related to the patient's prior use of antipsychotic medications included 1) a dichotomous variable indicating that two or more medications were used as initial therapy; 2) a set of dichotomous variables indicating the types of medications used in the prior 6-month period (typical antipsychotics, atypical antipsychotics, mood stabilizers, antidepressants, and depot formulations); 3) the number of psychotropic drug treatment episodes initiated in the prior 6 months; and 4) the number of days between episodes (included in the analysis of restart episodes only).

Statistical methods

The statistical approach that was used varied depending on the outcome measure being analyzed. Ordinary least squares (OLS) regression models were estimated for continuous outcome variables; Cox proportional hazard models were estimated for time-to-event outcome measures and logistic regression models were estimated for dichotomous outcome variables. Adjustments in the OLS estimated standard errors for multiple observations (episodes) per patient were applied using methods developed by White [10]. Other statistical methods, such as patient fixed-effects models, could not be used as an estimation strategy due to the methods used to create units of observation covering all treatment attempts by the patient. This focus on accuracy and completeness of the episode definition process resulted in overlapping episodes of unequal length. This data structure does not fit in the typical repeated measures framework on which fixed-effects and other methods are designed to work. Most researchers have overcome these challenges by limiting the range of episodes included in their research, which would defeat the purpose of this research.

Results

Baseline descriptive statistics

The descriptive statistics for episodes of treatment initiated by patients with a diagnosis of schizophrenia are displayed in Table 1. The study population of 5,909 patients initiated a total of 21,570 patient episodes, which met the inclusion and exclusion criteria for this study. The first observed episode for each of the 5,909 patients was excluded.

Several results are of interest. Patients were defined as having schizophrenia if they received a diagnosis of schizophrenia at any time in the data period. The data on the initial drug used in these episodes suggest that several of these patients may have been treated for possible bipolar disorders. Specifically, mood stabilizers and antidepressants make up approximately 27% and 38% of the drug therapy episodes initiated by these patients with a schizophrenia diagnosis. The use of nonantipsychotic medications is most pronounced in episodes in which two or more drugs are filled on the index date for the episode (combination therapy) with 54% and 64% of all combination episodes including these medications, respectively.

There are significant differences in the characteristics of patients by episode type. Patients initiating switching episodes tend to be younger than patients restarting or augmenting therapy; patients restarting therapy using the same medication are more likely to be greater than 65 years old when compared with patients augmenting or switching therapies. Patients restarting therapy also use risperidone and typical antipsychotics more frequently than in other episode types, have fewer prior episodes of treatment using a psychotropic drug, and cost about half as much as patients initiating an augmentation or switching episode in the 6 months prior to treatment initiation.

Combination episodes are much more likely to include risperidone (23%), quetiapine (18.7%), aripiprazole (14.2%), or conventional antipsychotics than olanzapine (3.4%), and ziprasidone episodes fall somewhere in the middle (9.7%). As noted before, the use of mood stabilizers and antidepressants is particularly high in combination episodes (54% and 64%, respectively).

Descriptive statistics for patient outcomes

Table 2 provides descriptive statistics for patient outcomes by episode type, and by combination versus monotherapy. Persistence with drug therapy differs significantly by episode type. Patients restarting a previous drug therapy exhibit significantly shorter TTAD whether measured for the initial drug (128 days vs. 183 for switch episodes and 197 for augmentation episode) or for all related psychotropic medications (172 days vs. 299 and 486 for switching and augmentation, respectively). Not surprisingly, patients initiating a restarting episode also had the lowest rate of 1

Table 1 – Baseline characteristics for patients with schizophrenia by episode type and number of drugs used as initial therapy: N = 21,570.

	Episode type			Number of initial drugs	
	Switch N = 4,633	Restart N = 3,486	Augmentation N = 13,451	Monotherapy N = 19,216	Combination therapy 2,354
Mean age (in years) [SD]	39.9 [15.7]	43.5 [15.6]	41.8 [15.4]	41.9 [15.6]	39.5 [14.6]
Age category (%)					
10–18 years old	8.3	3.8	6.6	6.5	6.8
18–25 years old	13.6	11.3	10.8	11.2	14.4
25–35 years old	14.6	12.2	13.4	13.4	14.1
35–45 years old	23.1	24.0	24.3	23.8	25.4
45–55 years old	23.7	25.9	25.5	25.2	25.0
55–65 years old	10.6	13.7	12.8	12.8	9.9
>65 years old	6.1	9.0	6.6	7.2	4.5
Male (%)	37.1	40.9	35.0	36.1	38.9
Initial drug number (%)					
Olanzapine	2.9	3.1	2.2	2.4	3.4
Risperidone	9.9	19.5	8.4	9.0	23.0
Quetiapine	9.3	9.1	9.8	8.5	18.7
Ziprasidone	5.3	4.4	4.4	4.0	9.7
Aripiprazole	10.9	8.2	7.0	7.3	14.2
Typical antipsychotics	5.9	18.0	6.2	7.5	12.7
Mood stabilizer	27.6	25.9	28.7	24.8	54.0
Antidepressant	37.3	36.7	39.4	35.4	63.9
Prior episode/year	1.63 [1.45]	1.00 [0.91]	2.48 [1.94]	2.15 [1.80]	1.28 [1.65]
Schizophrenia Dx (prior 6 months) (%)					
Acute	2.4	1.7	1.5	1.7	1.9
Simple	1.3	1.5	1.0	1.2	0.4
Catatonic	0.7	0.3	0.3	0.4	0.3
Disorganized	0.5	0.8	0.6	0.6	0.3
Latent	0.5	0.9	0.5	0.6	0.6
Paranoid	14.3	21.6	12.0	14.3	11.9
Residual	1.7	3.5	1.7	2.1	1.6
Schizo-affective	27.4	29.0	32.9	31.2	29.7
Not otherwise specified	13.1	13.9	13.5	13.7	11.9
Prior use ($/6 months)					
Ambulatory care	6,919 [11,209]	4,471 [9,699]	7,325 [11,794]	6,717 [11,478]	7,260 [10,736]
Prescription drugs	2,791 [2,702]	2,130 [2,032]	4,115 [3,271]	3,544 [3,121]	3,233 [2,821]
AP drug cost	1,144 [1,370]	937 [1,180]	1,720 [1,811]	1,480 [1,685]	1,383 [1,511]
Acute hospital care (%)	40.3%	19.1%	35.5%	32.2%	48.0%
Acute hospital care	9,271 [21,381]	3,857 [14,180]	7,969 [19,560]	7,100 [18,623]	11,535 [23,704]
Costs net of Rx	17,334 [28,305]	9,265 [19,587]	17,014 [26,710]	15,298 [25,656]	20,177 [30,051]
TOTAL COST	20,125 [29,132]	11,395 [20,068]	21,129 [27,601]	18,841 [26,586]	23,410 [30,723]

AP, antipsychotic; Dx, diagnosis; Rx, prescription.

year persistence on their initial drug (10%) or on all related psychotropic drugs (17.2%), and they had the lowest switch rates of all three episode types. Equally important, patients restarting their previous therapy also exhibited the lowest cost in the 1-year post-treatment period.

Differences in patient outcomes are much less pronounced when comparing monotherapy episodes with combination therapy. Probably the most significant difference in patient outcomes are that patients initiating with two or more drugs were more likely to be hospitalized in the first post-treatment year (42.2% vs. 34%) and experienced higher costs ($12,806 vs. $9,413 [USD]) relative to patients initiating treatment on monotherapy.

Multivariate results

The OLS models for the impact of treatment history on the patient outcomes achieved by patients with schizophrenia are presented in Table 3 and the logistic and Cox models are presented in Table 4. Augmentation episodes and combination therapy are the comparison groups. Only the results for the treatment history variables are presented due to space limitations. Results from the full models are available from the corresponding author.

Impact of episode type on patient outcomes

Episode type has a significant and large impact on measures of patient drug therapy compliance when compared to episodes of augmentation therapy. Patients restarting therapy using a drug used in their most recent prior treatment attempt terminate their initial therapy nearly 83 days sooner than patients initiating an augmentation episode. When measured over all related psychotropic medications, this difference increases to 273 days in a sample of patients required to only have a minimum of 360 days of data. Results for switching episodes are similar but less dramatic: 22 fewer days of therapy on the initial medication used in the switching episode and 155 fewer days of continuous therapy measured across all relevant drugs. A shorter duration of therapy in restart and switching episodes, however, does not result in higher costs. Patients restarting or switching therapy are consistently less costly to treat than patients augmenting therapy (<$7186 and

Table 2 – Drug therapy outcomes and post-treatment health-care cost for patients with schizophrenia by episode type and number of drugs used as initial therapy: N = 21,570.

	Episode type			Number of initial drugs	
	Switch N = 4,633	Restart N = 3,486	Augmentation N = 13,451	Monotherapy N = 19,216	Combination therapy 2,354
Duration of therapy (TTAD)					
Initial therapy	183 [196]	128 [171]	197 [214]	178 [203]	224 [219]
All related drugs	299 [269]	172 [225]	486 [296]	399 [307]	362 [293]
Completed 360 days of therapy (%)					
Initial therapy	16.2%	10.0%	18.3%	15.8%	22.2%
All related therapy	34.5%	17.2%	63.3%	50.2%	45.2%
Switched/augment within 1 year (%)	53.2%	28.1%	44.4%	42.7%	51.2%
Post-treatment costs (1 year) ($)					
Ambulatory care	10,887 [20,297]	7,910 [17,603]	12,767 [20,196]	11,503 [19,777]	12,195 [20,878]
Prescription drugs	4,969 [5,158]	3,802 [3,797]	7,842 [6,183]	6,601 [5,905]	6,334 [5,751]
AP drug cost	2,147 [2,662]	1,766 [2,396]	3,343 [3,442]	2,832 [3,208]	2,826 [3,202]
Hospital admission within 1 year (%)	35.7%	23.9%	37.4%	34.0%	42.2%
Acute hospital costs	10,002 [25,652]	5,865 [18,526]	10,723 [26,599]	9,413 [24,521]	12,806 [30,905]
Costs net of Rx	23,035 [39,496]	15,542 [30,663]	26,833 [39,892]	23,748 [37,839]	27,827 [44,794]
TOTAL COST	28,004 [41,261]	19,344 [31,893]	34,675 [41,892]	30,348 [39,954]	34,161 [46,217]

AP, antipsychotic; Rx, prescription; TTAD, time to all-cause discontinuation.

<$4441 [USD], respectively, $P < 0.0001$ for both estimates). The lower cost in restart and switching episodes is consistent across all type of services except for acute hospital care, which is significantly higher for patients who restart therapy (>$1684 [USD], $P < 0.0001$).

In general, the OLS results in Table 3 are confirmed by the logistic and proportional hazard analyses of events reported in Table 4. Patients initiating a restart or switching episode are less likely to complete one year of uninterrupted drug therapy and more likely to discontinue therapy than patients initiating an augmentation episode. Patients initiating a switching episode, however, are significantly more likely to switch again within 1 year than patients augmenting a pre-existing therapy (odds ratio = 1.56; hazard ratio = 1.41, $P < 0.0001$ for both estimates). Patients restarting therapy are less likely to be admitted to an acute hospital than patients initiating an augmentation episode (odds ratio = 0.74; hazard ratio = 0.76, $P < 0.0001$), yet their cost for hospital care was found to be significantly higher than patients augmenting therapy (Table 3).

Other treatment history factors

The impact of monotherapy relative to combination therapy displays a pattern similar to the impact of episode type. Monotherapy is associated with shorter duration of therapy and lower post-treatment costs with the exception of significantly higher acute hospital costs. Conversely, the number of treatment attempts in the prior 6 months is positively correlated with duration of therapy and with higher costs across all types of service. Finally, the mix of drugs used in the prior 6 months has a mixed but significant impact of patient outcomes. Patients with a history of using an antipsychotic medication in the prior 6 months are consistently less compliant and less costly to treat in the first post-treatment year. Patients with a history of antidepressant use are also less compliant but the impact of prior antidepressant use on post-treatment cost is mixed. Patients with schizophrenia with a history of mood stabilizer use within 6 months of initiating an episode of therapy are less compliant and more costly to treat.

The pattern of estimated effects for monotherapy, prior drug used, depot therapy, and number of episodes of drug therapy

Table 3 – Estimates of patient history variables on days of therapy and post-treatment costs: patients with schizophrenia: all treatment episodes: N = 21,570.

Drug treatment history	Duration on initial AP $R^2 = 0.0544$	Duration on all drugs $R^2 = 0.2115$	Ambulatory costs $R^2 = 0.2146$	Drug costs (all Rx) $R^2 = 0.2218$	Antipsychotic drug cost $R^2 = 0.1516$	Hospital costs $R^2 = 0.1090$	Net costs $R^2 = 0.1978$	Total costs $R^2 = 0.2182$
Episode type (vs. augmentation)								
Restart	−82.9*	−273.0*	−1597*	−2722*	−1183*	1684*	−4463*	−7186*
Switch	−21.6*	−154.9*	−818†	−2137*	−994*	492	−2304‡	−4441*
Monotherapy (vs. combination therapy)	−30.3*	−12.3	501	−295	−347*	2039†	−1885	−2180
Prior drug use (6 months)								
Typical antipsychotics	−19.3*	−13.4†	−1223‡	−736*	−121	−109	−1453	−2189‡
Atypical antipsychotics	−24.4*	−34.6*	−2220*	429*	1061*	−1716*	−2875*	−2447*
Antidepressants	−41.6*	−46.7*	888‡	−228‡	−413*	350	826	597
Mood stabilizers	−31.6*	−2.4	1079*	769*	−71	794†	1802‡	2572*
Depot AP prior	37.0	31.3	7913†	1616‡	1872*	6000	15784‡	17401*
Number of prior episodes	5.74*	30.29*	138.74*	279.68*	111.25*	198.80*	448.79*	728.47*

AP, antipsychotic; Rx, prescription.
* $P < 0.0001$; † $P < 0.05$; ‡ $P < 0.01$.

Table 4 – Estimates of patient history variables on event outcomes: patients with schizophrenia: all treatment episodes: N = 21,570 (5,909 patients).

Independent variables	Logistic regression models (Odds ratios vs. TAP)				Cox proportional hazards models (Hazard ratios vs. TAP)			
	Duration on initial >360 days	Duration on all >360 days	Switched/ augment w/i 1 year	Acute hospital admission w/i 1 year	Time to D/C initial Rx	Time to D/C all Rx	Time to switch in Rx	Time to acute hospital admission
	Pseudo R^2=0.0393	Pseudo R^2=0.1244	Pseudo R^2=0.0386	Pseudo R^2=0.0831				
Episode type (vs. augment)								
Restart	0.46†	0.16†	0.77†	0.74†	1.58†	3.44†	0.85†	0.76†
Switch	0.78†	0.34†	1.56†	.096	1.12†	1.97†	1.41†	1.03
Mono-therapy (vs. combination therapy)	0.74†	0.88	0.79‡	0.74†	1.13‡	1.05	0.85‡	0.76†
Prior rx use (6 mos.)								
Typical antipsychotics	0.88	1.01	0.95	0.99	1.10‡	1.03	0.98	0.91
Atypical antipsychotics	0.83†	0.95	0.89‡	0.82†	1.11†	1.08*	0.92‡	0.85†
Antidepressants	0.69†	0.82†	1.05	1.03	1.21†	1.11‡	1.07*	0.95
Mood stabilizers	0.81†	1.15‡	1.17†	1.11	1.16†	0.93*	1.14†	1.07
Depot AP prior	1.18	1.48	0.95	1.10	0.87	0.76	0.97	1.03
Number of prior episodes	1.02	1.073†	1.080†	1.065†	0.986*	0.957†	1.053†	1.087†

* $P < 0.05$; † $P < 0.0001$; ‡ $P < 0.01$.

(Table 3) were generally confirmed by the logistic and proportional hazard model results found in Table 4. Patients with a history of atypical antipsychotic drug use are less likely to switch medications and are less likely to be admitted to the hospital in the post-treatment period. Conversely, patients with a history of mood stabilizer use are more likely to switch and are more likely to be admitted to an acute hospital.

Comparative effectiveness comparisons

Impact of treatment history

This research found that a patient's drug treatment history has a significant and clinically important impact on patient outcomes (Tables 3 and 4). Moreover, treatment history also varies significantly across alternative medications (Table 1). Taken together, these results suggest that head-to-head comparisons across alternative drugs could be significantly biased if these analyses do not take treatment history into account, which is common in most retrospective database comparisons of drug performance [3–6].

The extent of possible bias in comparisons across the alternative drugs in the treatment of patients with schizophrenia is presented in Table 5. The "no history" model parallels "usual practice" and includes only a set of dichotomous variables for the specific drug used as initial therapy (typical antipsychotics [TAP] as the comparison group). The model with treatment history includes variables for episode type (in the all episodes analysis), monotherapy, mix of prior drugs, and number of episodes in the prior 6 months.

All episodes

Standard estimation models for TTAD patient outcomes that do not include variables related to patient treatment history favor the atypical antipsychotics relative to TAP – between 11 days for risperidone and 61 days for ziprasidone. These results also hold for comparisons of mood stabilizers (>45 days) and antidepressants (>26 days) as initial therapy relative to TAP. The gaps in TTAD favoring the atypical antipsychotics relative to TAP are significantly reduced when treatment history variables are added to the analysis and, in the case of olanzapine and risperidone, favorable TTAD effects disappear entirely. Conversely, the estimated impacts of the atypical antipsychotics on health-care costs relative to TAP improve when the independent variables for patient treatment history are included in the analysis. For example, in the model with no treatment history, quetiapine was estimated to increase total cost by $4022 (USD; $P < 0.0001$). This estimate dropped to greater than $3135 (USD; $P < 0.01$) when the drug treatment variables are included in the analysis.

By episode type

One way to take patient treatment history into account is to conduct separate analyses by episode type. These analyses are reported in the bottom three panels in Table 5. In these models, the treatment history variables for monotherapy, dummy variables documenting the patient's use of medications in the prior 6 months, and the number of episodes initiated per year prior to the episode index data are again left out of the "no history" models.

Leaving out the treatment history variables consistently favors the atypical antipsychotics when compared to TAP for TTAD across all episode types. The bias introduced by leaving out treatment history variables is less clear, however, in the cost analyses. In general, the inclusion of treatment history variables results in larger estimated cost increases for the atypical antipsychotics relative to TAP in restart episodes. The opposite is true in switching and augmentation episodes because including treatment history improved the estimated cost impact of using an atypical antipsychotic relative to TAP. What is particularly interesting is the fact that those atypical antipsychotics with no TTAD benefit relative to TAP (olanzapine, risperidone) have the best cost profile of all of the atypical antipsychotics.

Discussion

Treatment history has a significant impact on the estimated comparative effectiveness of atypical antipsychotics relative to conventional antipsychotics using retrospective data. The implications of ignoring treatment history are particularly evident in comparative effectiveness as measured by TTAD. Specifically, the new antipsychotics appear to achieve longer TTAD if the estima-

Table 5 – Sensitivity of comparative effectiveness results comparing antipsychotics to model specifications with/without independent variables for treatment history [TAP as comparison drug].

	Duration on initial AP		Total costs ($/year)	
	Model with no drug history variables	Model with drug history variables	Model with no drug history variables	Model with drug history variables
All episodes: N = 21,570	$R^2 = 0.0282$	$R^2 = 0.0544$	$R^2 = 0.2081$	$R^2 = 0.2182$
Olanzapine	14.7	−8.4	569	205
Risperidone	11.1*	−1.8	−653	−217
Quetiapine	44.5†	23.6†	4022†	3135‡
Ziprasidone	60.5†	39.9†	3635*	3178*
Aripiprazole	51.1†	30.8†	1982	1811
Mood stabilizer	45.1†	25.4†	4013†	2312*
Antidepressant	25.6†	5.7	1605*	343
Restart episodes: N = 4,633	$R^2 = 0.0473$	$R^2 = 0.0812$	$R^2 = 0.2124$	$R^2 = 0.1934$
Olanzapine	46.7*	−9.5	610	289
Risperidone	24.0*	−2.3	−1523	864
Quetiapine	63.7†	9.4	9620†	5524*
Ziprasidone	44.0‡	8.1	580	5174
Aripiprazole	62.0†	4.8	2237	2427
Mood stabilizer	53.6†	34.1‡	2593	3290
Antidepressant	22.4‡	4.6	391	503
Switching episodes: N = 3,486	$R^2 = 0.0801$	$R^2 = 0.0851$	$R^2 = 0.2105$	$R^2 = 0.2401$
Olanzapine	−1.0	−13.8	−484	−576
Risperidone	28.7†	−23.2	1643	−2662
Quetiapine	38.2†	27.0	5179*	8039‡
Ziprasidone	34.2*	0.8	4683	−1764
Aripiprazole	18.1	18.3	2580	1515
Mood stabilizer	47.6†	8.8	5943†	656
Antidepressant	33.8†	−20.9	2665	−434
Augmentation episodes: N = 13,451	$R^2 = 0.0323$	$R^2 = 0.0441$	$R^2 = 0.2134$	$R^2 = 0.2162$
Olanzapine	17.2	−12.1	1630	359
Risperidone	20.0‡	−0.9	274	−585
Quetiapine	44.4†	22.7*	2451	1573
Ziprasidone	79.3†	57.5†	4751*	3866
Aripiprazole	64.0†	40.5†	2362	1471
Mood stabilizer	46.7†	25.8‡	4128†	2888*
Antidepressant	29.9†	8.6	1851	820

AP, antipsychotic; TAP, typical antipsychotics.
* $P < 0.05$; † $P < 0.0001$; ‡ $P < 0.01$.

tion models ignore treatment history. This bias becomes even more pronounced when the analyses are restricted to patients with breaks in therapy [washout periods]. Ignoring treatment history, however, makes the newer medications appear to be more costly in these retrospective comparative effectiveness comparisons with the exception of restart episodes.

Full transparency requires that a study should document the patient's treatment history and then use these variables to control for the effects of treatment history of comparative effectiveness. This approach was used by Chen et al. [1,2] when comparing olanzapine, risperidone and quetiapine to TAP using Medicaid data from California. A total of 219,504 episodes of antipsychotic therapy were included in the analysis. Their results indicate that treatment history has a significant impact on TTAD and post-treatment costs. Unlike the results reported here, however, the atypical antipsychotics were consistently associated with longer TTAD than TAP for all episode types, ranging from 13 to 15 days for restart episodes and 31 to 38 days for augmentation episodes. Differences across the atypical antipsychotics were small. The atypical antipsychotics were also associated with lower cost in restart and augmentation episodes, but not switching episodes.

The results reported here and in Chen et al. [1,2] should engender concern on the part of clinicians, pharmacy and therapeutics committees, HMOs, insurance companies, and government programs about possible bias in retrospective database research that is narrow in scope and/or fails to take into account patient treatment history. This concern should extend beyond severe mental disorders to include any disease state in which long-term drug therapy is indicated but difficult to achieve. Hopefully, the standard of practice for observational research will move toward including the full range of treated patients and accounting for each patient's treatment history in their analyses.

Clinicians, pharmacy and therapeutic committees, health insurance companies, HMOs and government programs must be aware of the potential for bias in comparative effectiveness research based on retrospective data. These studies typically consider very restricted sub-samples of all observable patient treatment episodes, focusing instead on patients with extended periods in which no relevant drugs are used. The potential for systematic bias is particularly troublesome in studies comparing only 2 to 3 antipsychotic drugs and requiring an extended washout period on these study drugs while allowing the prior use of other medications. For example, Rascati et al. [3] compared olanzapine (n = 1906) and risperidone (n = 979) using Texas Medicaid data for patients with schizophrenia newly started on these products. Patients being treated with olanzapine were less likely to discontinue treatment during the first year (8.89% vs. 14.51%, $P < 0.0001$) and had more days of therapy in the first year (248 days vs. 211

days, $P < 0.0001$) than risperidone patients. Gibson et al. [4] compared episodes of drug therapy for Michigan Medicaid patients with schizophrenia treated with olanzapine (n = 458), risperidone (n = 481) or haloperidol (n = 252). A 6-month washout period was required between episodes using the same drug (a restart episode) and a 30-day washout period was required for the other study drugs (a delayed switching episode). Fifty-nine percent (59%) of olanzapine patients were taking a concomitant non-study antipsychotic at the start of the episode (switching or augmentation episodes) compared with 39% of risperidone patients. Unadjusted TTAD data did favor olanzapine over risperidone (166 days vs. 128 days) whereas compliance with haloperidol was significantly worse relative to both olanzapine and risperidone. Finally, Yu, et al. [5] selected adult patients with schizophrenia from the Pennsylvania Medicaid program. The study was limited to patients who initiated either olanzapine or quetiapine monotherapy after a 90-day washout period on these drugs, although prescriptions using other antipsychotics were allowed during this period. Propensity score methods were used to match patients and data on treatment history were included in the propensity model for the use of quetiapine. Olanzapine patients were estimated to be less costly relative to quetiapine patients primarily due to reduced hospitalization costs.

Limitations

Analyses based on paid claims data have a host of limitations that must be considered in interpreting their results. First, clinical data documenting potential differences in severity of illness and sensitivity to side effects across alternative drugs are not available on paid claims. For example, it may be the case that patients who initiate augmentation episodes are more severely ill and thereby motivated to maintain continuous therapy. Patients who use drug therapy intermittently (restart episodes) may be less severely ill or may experience more symptom-free periods during which they do not consume high levels of health-care services.

Using the gap of 15 days to define discontinuation of drug therapy can be debated. For restart episodes, substituting an alternative gap of 30 days would collapse sequential restart episodes separated by 16 to 30 days into a single episode and increase the average duration of therapy. It is unclear whether or not this change would favor one drug or class of drugs over another. Unfortunately, conducting sensitivity analyses of different definition of gaps in treatment used to define episodes cannot be accomplished by simply toggling between different definitions. Each alternative definition of the maximum gap allowed in defining discontinuation of therapy would require that the entire data set be reconstructed.

This analysis also dropped all first observed episodes due to possible left-censoring of the data, which made it impossible to document the treatment history of the episode. One could select only those first observed episodes with 6 months to 1 year of pretreatment data with no antipsychotic drug use for separate analyses. This sensitivity analysis was beyond the scope of this study, which focused on the impact of missing treatment history on patient outcomes. Moreover, there are several studies already in the literature that use this selection process to simplify the statistical methods they apply in their studies.

Source of financial support: The data set used in this research was developed as part of a research grant from Bristol-Myers Squibb (BMS) to the University of Southern California, which retains the unrestricted publication rights to all research findings.

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